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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/029,598	12/21/2001	Ching-Leou Teng	ISIS-4945	6046

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EXAMINER	
EPPS, JANET L	

ART UNIT	PAPER NUMBER
1635	9

DATE MAILED: 02/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/029,598	TENG ET AL.	
	Examiner	Art Unit	
	Janet L Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 27-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 27-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-15 and 27-31 in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1, 3, 8-12, and 14-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Bennett et al. (US Patent 5,843,738)

4. Claims 1, 3, and 8-10 recite an oligonucleotide formulation suitable for rectal delivery, wherein said formulation is a suppository, wherein said oligonucleotide is an antisense oligonucleotide, wherein said antisense oligonucleotide modulates expression of a cellular adhesion protein, wherein said antisense oligonucleotide modulates a rate of cellular proliferation or has biological activity against eukaryotic pathogens or retroviruses. Claims 11-12 recite the formulation of claim 9, wherein said cellular adhesion protein is ICAM-1, and wherein the oligonucleotide of the formulation of claim 1 has the sequence shown in SEQ ID NO: 1. Claims 14-15 recite the formulation of claim 1, further comprising at least one penetration enhancer,

wherein the penetration enhancer is a fatty acid, bile salt, chelating agent, surfactant or non-chelating non-surfactant.

Bennett et al. disclose antisense oligonucleotides targeted to mRNA corresponding to the cell adhesion molecule human ICAM-1, and specifically wherein said antisense oligonucleotide has a sequence according to SEQ ID NO: 1. Additionally, Bennett et al. disclose compositions comprising said antisense oligonucleotides for rectal and oral administration (col. 9, line 11-15), and further wherein said antisense oligonucleotide comprises modified base modifications (col. 9, lines 46-48), sugar modifications (col. 10, lines 5-19), and phosphorothioate modifications (col. 9, lines 53-67). The modifications to the base, sugar and internucleoside linkage are preferred over native forms because of properties such as, for example, enhanced cellular uptake and increased stability in the presence of nucleases (col. 9, lines 49-51). The compositions for oral administration include capsules and tablets, wherein emulsifiers, dispersing agents, and diluents may be added (col. 9, lines 24-26). Formulations for topical administration include ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders (see col. 9, lines 18-20). In one particular example, Bennett et al. discloses formulations comprising an antisense oligonucleotide targeting ICAM-1 and the cationic lipid Lipofectin (col. 25, lines 60-64), Opti-MEM/DOTMA (col. 12, lines 59-62), and DOTMA/DOPE (col. 26, line 57).

Bennett et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

5. Claims 1-15, and 32 are rejected under 35 USC 102(e) as being anticipated by Bennett et al. (US 6,096,722).

Bennett et al. teach oligonucleotide formulations for the modulation of expression of cellular adhesion molecules that are suitable for rectal delivery. The formulations of Bennett et al. include an enema, a suppository, a saline solution, and a buffered solution. The antisense oligonucleotides of Bennett et al. include ISIS 2302 (see Table 1, line 43). The formulations of Bennett et al. also include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (col. 15, lines 5-9).

Bennett et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

6. Claims 27-29 are rejected under 35 USC 102(e) as being anticipated by Werner et al.

Claims 27 are drawn to a composition comprising at least one oligonucleotide in an emulsion and at least one penetration enhancer selected from the group consisting of surfactants, fatty acids, bile salts, chelating agents, non-chelating non surfactant molecules, and combinations thereof; wherein said oligonucleotide is selected from the group consisting of a molecular decoy, an external guide sequence and an aptamer. Claim 28 recites the composition of claim 27 further comprising a carrier compound, wherein said carrier compound is selected from the group consisting of lipofectin, cationic glycerol derivatives, and polylysine. Claim 29 recites a composition comprising an oligonucleotide in oral dosage form, wherein said oligonucleotide comprises at least one modified covalent linkage and wherein said oligonucleotide is selected from the group consisting of a molecular decoy, an external guide sequence and an aptamer.

Werner et al. teach the delivery of external guide sequence molecules (EGS) as a complex with heme lipid particles, wherein the complex comprises DOPE and DOTAP (surfactant type penetration enhancers and cationic glycerol derivatives), and prepared as an emulsion (col. 10, lines 6-28). Additionally, the EGS molecules of Werner et al. may include chemical modifications that greatly enhance the biological function of the EGS. For example, they may include 2'-methoxy ribonucleotides, and phosphorothioate nucleotides (see col. 11, lines 1-4).

Werner et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

7. Claim 30 is rejected under 35 USC 102(e) as being anticipated by Manair et al.

Claim 30 recites a composition in oral dosage form comprising a modified oligonucleotide and enteric material selected from cellulose acetate trimellitate, hydroxy propyl methylcellulose phthalate, and cellulose acetate phthalate.

Manair et al. disclose compositions comprising therapeutically active biopolymers such as an oligonucleotide, wherein said biopolymer can consist of base analogs, and may comprise a thioester linkage (col. 3, lines 34-42). These compositions may be administered orally, (col. 2, line 35). The compositions of the invention may include a coating, wherein the coating may include cellulose actate phthalate (col. 9, lines 15-20).

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 12-13, 28 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 recites the limitation "said antisense." There is insufficient antecedent basis for this limitation in the claim.

Claim 13 recites the limitation "said enema." There is insufficient antecedent basis for this limitation in the claim.

Claim 28 recites the trademark name "lipofectin." Claim 31 recites the trademark name "precirol." In the instant case, the recitation of these trademark names renders the scope of claims 28 and 31 uncertain as per MPEP § 2173.05(u) since the trademark or trade name cannot be used properly to identify any particular material or product. Additionally, the specification as filed does not provide a description of the product represented by these trademark names in generic terms. Therefore, since the scope of claims 28 and 31 are uncertain, these claims fail to provide clear warning to others as to what constitutes infringement of the claimed invention.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 9-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description)

The instant claims recite wherein said antisense oligonucleotide modulates expression of a cellular adhesion protein, and wherein said antisense oligonucleotide modulates a rate of cellular proliferation or has biological activity against eukaryotic pathogens or retroviruses. The scope of the claimed invention encompasses antisense oligonucleotides that modulate (*i.e. increase or decrease*) expression of a broad genus of genes encoding cellular adhesion proteins, and antisense oligonucleotides that modulate a rate of cellular proliferation (or genes that control a rate of cellular proliferation) and antisense oligonucleotides that have biological activity against eukaryotic pathogens or retroviruses. The antisense oligonucleotides recited in the instant claims encompasses all sequences from other species, mutated sequences, polymorphic, allelic and splice variants, and sequences that have an unspecified degree of identity (similarity, homology), and so forth. However, this broad genus of antisense oligonucleotides is not properly described in the specification as filed.

The specification as filed provides several representative antisense oligonucleotides encompassed by the claimed invention which target various cell adhesion proteins, see page 30 of specification. However, the structure of these antisense oligonucleotides do not allow one of skill in the art to predict the structures of the full scope of antisense compounds encompassed by the claimed invention, nor is any guidance given in this regard.

See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed

invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

Additionally, "[T]he skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required." See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483.

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Therefore, the specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of these compounds at the time of filing of this application. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 9:00AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
February 5, 2003

SEAN McGARRY
PRIMARY EXAMINER